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(54) Title: COMPOSITION AND METHOD FOR NEURAL DESENSITIZATION

(57) Abstract

The invention consists of a composition and method for desensitizing sensory neurons by administration of therapeutic amounts of resiniferatoxin.

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COMPOSITION AND METHOD FOR NEURAL DESENSITIZATION

Background of the Invention

This invention relates generally to a composition and method for desensitization of peripheral nerves. More particularly, this invention relates to the use of resiniferatoxin to desensitize primary afferent neurons of the mammalian body. The primary afferent neurons are located outside the central nervous system and convey information about the state of the peripheral environment to the central nervous system. These sensory cells are located in the dorsal ganglia along the spinal cord. The primary afferent neurons express peripheral processes to the specific areas, e.g. visceral organs, skin, joints, blood vessels, etc. The peripheral processes contain special sensory receptors which detect various physicochemical stimuli such as temperature, pressure, pain, inflammation, chemical irritation, movement, stretching, etc at the local area. When a particular activating stimulus is recognized, a neuronal impulse is generated and transmitted throughout the cell's central process into the spinal cord where the information is transmitted to the brain. The overall pattern of this incoming information allows the brain to monitor and react to a wide range of stimuli both inside and outside the body. Reaction to the stimuli may be voluntary, e.g., the micturition response of the bladder to stretching from fullness, or involuntary, e.g., reflexive withdrawal of the hand from heat.

Much of the discomfort arising from human disease originates with the sensory neural systems. While the sensory discomfort initially indicates to the brain that an abnormality exists, the

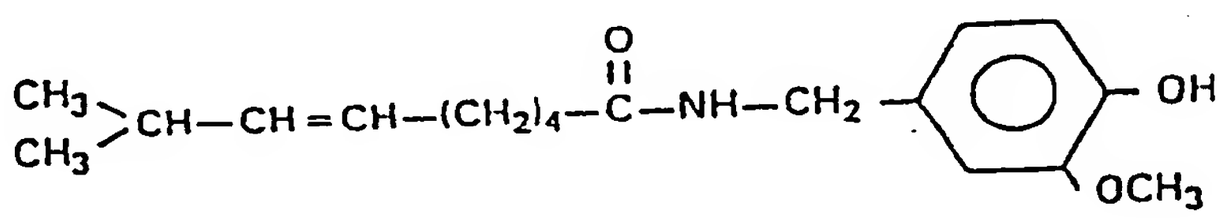
lasting discomfort usually becomes the most serious symptom of the disease. Indeed, in certain cases, such as urge incontinence and many sensory polyneuritic/neuropathic disorders, the sensory neural systems are believed the primary disease site. The critical nature of sensory neural systems as sites for drug action is indicated by the billions of dollars spent each year on pain relief substances, e.g., opiates, nonsteroidal anti-inflammatory agents, aspirin and related substances, local anesthetics, etc. However, each of these current approaches to pain therapy suffer from at least one of the following: limiting side-effects, lack of target specificity, lack of strong efficacy or short duration of action. Thus, there is a very substantial need for therapeutic compounds which exhibit strong and specific actions of long duration on the sensory neural systems.

Discovery and identification of therapeutic agents exhibiting strong and specific action on the primary afferent neurons has been difficult due to the fact that the specific neurotransmitters and neuromodulators of the sensory neurons had been a mystery. Recently, certain neuropeptides have been implicated in sensory neuron activity. The scientific literature has implicated substance P, neurokinin A and other tachykinins, eledoisin-like peptide, somatostatin, vasoactive intestinal polypeptide, cholecystokinin-octapeptide, calcitonin gene-related peptide, galanin, corticotropin-releasing factor, arginine vasopressin and bombesin-like peptides in sensory neuron activity. (Maggi, C.A., et al, "The sensory-efferent function of capsaicin-sensitive sensory neurons," Gen. Pharmac., 19: 1-43, 1988).

In an effort to harness the neurochemical activity and control

sensory neurons, pharmaceutical compositions of capsaicin (8-methyl-N-vanillyl-6-noneanamide), the active ingredient of hot peppers of the plant genus Capsicum, have been developed. U.S. Patent No. 4,313,958 issued to Thomas LaHann on February 2, 1982, teaches the analgesic activity of systemic and topically applied capsaicin. U.S. Patent NO. 4,486,450 issued to Joel E. Bernstein on December 4, 1984 discloses the antipsoriatic activity of topically applied capsaicin. Finally, U.S. Patent No. 4,536,404 also issued to Joel E. Bernstein on August 20, 1985 discloses the use of topically applied capsaicin for treatment of post-herpetic neuralgia.

Capsaicin has the following structure:



A substantial body of work relating to the mechanism of action of capsaicin on sensory nerves is described in the literature. It is well know that application of capsaicin exhibits unique action on certain sensory neurons which involves an initial painful excitation followed by a long-lasting desensitization. During this desensitization, the affected neurons are insensitive to irritant and other painful stimulation, as well as to their natural physicochemical stimuli, i.e., heat, chemical irritation, certain visceral reflex signals, allergic reactions, and other forms of pain and inflammation. (Buck, S.H. et al, Pharmacological Reviews, 38: 179-226, 1986). Sensory pain fibers are generally referred

to as myelinated, fast conducting A-fibers and unmyelinated, conducting C-fibers. Capsaicin appears to act primarily on the sensory neurons with unmyelinated C-fibers. It is widely accepted that capsaicin acts as a specific neurotoxin on the type "C" primary afferent fibers subserving a sensory function on the afferent limb of various cardiorespiratory reflexes. It has been postulated that capsaicin causes changes in the permeability of the sensory neuron membrane which results in the initiation of an impulse. This impulse results in the release of neurotransmitters such as substance P, and other substances, causing an activation of the primary afferent system manifested by an initial burning pain, irritation and redness. Repeated application of capsaicin, however, causes depletion of substance P from the neuron and subsequent tachyphylaxis. (Drug Intelligence and Clinical Pharmacy, 22:488 June, 1988).

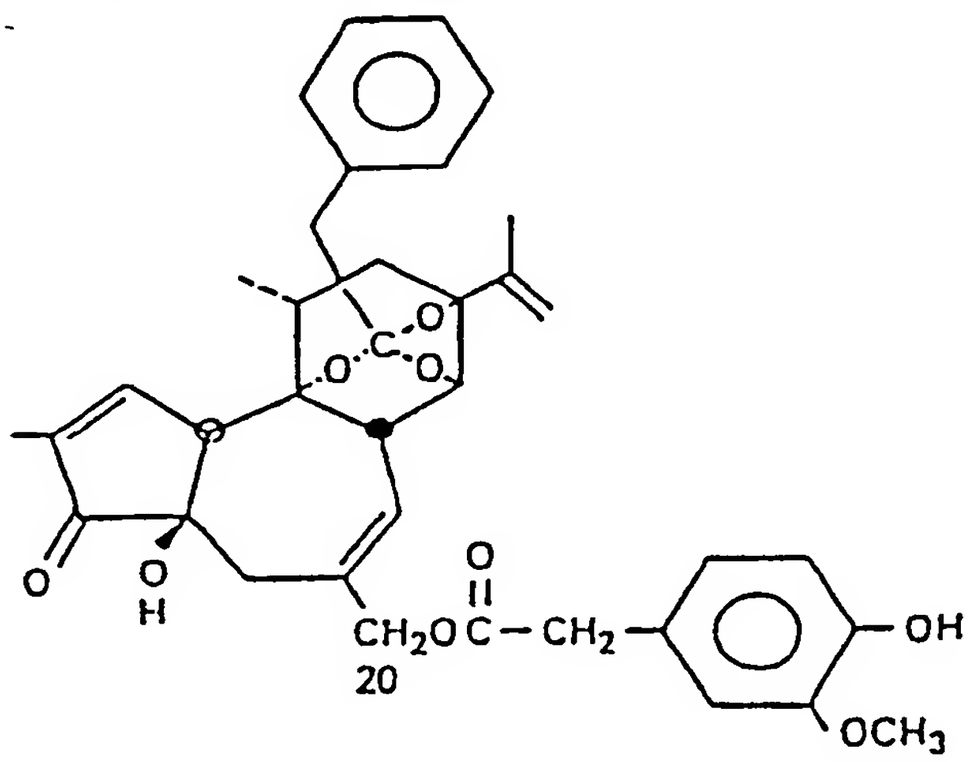
The literature describes the efficacy of topically applied capsaicin in vasomotor rhinitis (Maraibini, S., et al, Reg. Peptides, 22:(1-2) 1988); an excitatory effect on micturition threshold by topical application of capsaicin to the urinary bladder (Maggi, C.A., et al., "The effects of topical capsaicin on rat urinary bladder motility in vivo," European J. Pharmacology, 103:41, 1984); and an excitatory effect on micturition threshold by intravesical administration of capsaicin (Santicioli, P., et al. "The effect of capsaicin pretreatment on the cystometrograms of urethane anesthetized rats," The Journal of Urology, 133:700-703 1985.) Capsaicin has also been demonstrated to exhibit desensitization of excised longitudinal muscle strips from human jejunum. (Magi, C.A. et al, "Specific motor effect of capsaicin

on human jejunum," European Journal of Pharmacology, 149:393-395 1988.) The desensitizing activity of capsaicin on a variety of tissues is disclosed by S.H. Buck and T.F. Burks in Pharmacological Reviews 38:179-226 1986.

Thus, the actions of capsaicin are similar to a long-lasting anesthetic, but with a much greater sensation-specific spectrum of action. Because of these desensitizing/analgesic properties, capsaicin has been introduced as a therapeutic agent in a topical ointment under the name Zostrix by GenDerm Corporation. Zostrix is currently undergoing testing for use in psoriasis, diabetic neuropathy, post-mastectomy pain, vulvar vestibulitis, reflex sympathetic dystrophy, trigeminal neuralgia and other disorders involving sensory neural systems.

Summary of the Invention

In accordance with the present invention, resiniferatoxin, a compound extracted from the plant genus Euphorbia which bears some structural resemblance to capsaicin through the presence of the hydroxy-methoxy phenyl moiety, exhibits desensitization of sensory neural systems potentially reduced initial irritant activity compared to capsaicin. Resiniferatoxin has the following structure:



Detailed Description of the Preferred Embodiment

Thus, in accordance with the present invention, resiniferatoxin, and its analogues, are to be employed for desensitizing primary afferent neurons implicated in the following, which are given as examples only and are not intended to limit the scope or content of the present invention: visceral/visceromotor indications, such as unstable bladder associated with urge and stress incontinence; dermatological inflammation/pain, such as herpetic lesions or dermatitis from psoriasis, eczema or allergy; neuropathic pain, such as post herpetic neuralgia; joint inflammation/pain; and respiratory disorders, such as rhinitis or hay fever, each of which might involve or be modified by desensitizing the primary afferent neuronal system subserving the specific body area.

Resiniferatoxin is an esterification product of resiniferonol-9,13,14-orthophenylacetate. The irritant activity of topically applied resiniferatoxin, the most potent ester, as well as other esters of resiniferonol-9,13,14-orthophenylacetate, has been known from some time. It is known that various esterifications of the C-20 position of resiniferonol alter the irritant activity of the molecule, with resiniferatoxin, where the C-20 moiety is (4-hydroxy-3-methoxy) phenyl acetate, having the greatest irritant activity of all C-20 esterification products. (Schmidt, R.J., et al "Investigations into the Skin-Irritant Properties of Resiniferonol Ortho Esters," Inflammation, 3:273-80 1979; Adolf, A., et al, "Structure-Activity Relations of Polyfunctional Diterpenes of the Daphnane Type. I. Revised Structure for Resiniferatoxin and Structure-Activity Relations of Resiniferonol

and Some of its Esters," J. Nat'l Prod. 45:347-54, 1982).

While the irritant activity of topically applied resiniferatoxin has been demonstrated, there has been no known evidence to suggest that resiniferatoxin would exhibit desensitizing activity on the primary afferent neural systems. While both capsaicin and resiniferatoxin share a (4-hydroxy-3-methoxy) phenyl moiety, the lack of similar activity for other neurochemicals having the same moiety, i.e., norepinephrine and dopamine, suggests the importance of other substituents as factors in desensitizing activity relative to the primary afferent neural systems. Moreover, the literature suggests that the absence of the acylamide linkage in capsaicin abolished the desensitizing activity of an ester-substituted capsaicin congener. (Szolesanyi, J., et al., "Sensory Effects of Capsaicin Congeners," Arzneim.-Forsch. (Drug Res.) 26:33-37 1976).

Thus, it is completely unclear whether the known irritant activity of resiniferatoxin would translate into desensitizing activity for the primary afferent neural systems. As indicated by the following test results, however, resiniferatoxin exhibits significant desensitizing activity in topical and visceral application to primary afferent neural sites.

To test the desensitizing activity of resiniferatoxin, three representative primary afferent neural sites were chosen: skin, cornea and bladder. The broad range of primary afferent neural desensitizing activity of resiniferatoxin by topical and visceral administrative routes will be readily appreciated by reference to the following animal experiments.

MOUSE SKIN TESTS

The right hind-paw of each of six ICR mice was lightly abraded with sandpaper to remove the superficial corneal skin layers and any oils and grease from the skin. The skin was not broken, nor was any blood visible. Immediately thereafter, the paw was bathed in 20 μl of a resiniferatoxin/acetone solution (0.4 μg resiniferatoxin/20 μl acetone). After seven minutes each mouse was scored for signs of discomfort to the paw. A positive score was obtained if the mouse showed signs of licking, biting or holding the paw above the cage floor. Each mouse was evaluated for ten seconds, once each minute for five minutes, for a maximum score of 5/5. After the five minute evaluation, the application of resiniferatoxin to each hindpaw was repeated. Again, seven minutes was allowed, whereafter each mouse was reevaluated for an additional five minute period. This procedure was repeated two additional times for a total of four repetitions.

After the first application of resiniferatoxin, the scores for individual mice showed progressive decreases in the number of positive responses. Desensitization was seen beginning with the third application. Significance was determined by ANOVA followed by Student's test and is established at 95% confidence.

The results of the scoring is summarized in Table 1.

TABLE 1

Application Number	Positive Responses (Mean + S.E.)
1	4 + 0.75
2	4.8 + 0.2
3	3.85 +0.75
4	0.6 +0.4

MOUSE CORNEA TEST

5 μl of a 10 μg/ml solution of resiniferatoxin (1% ethanol) instilled onto the cornea of each of five ICR mice four times at fifteen minute intervals. Fifteen minutes after the last application, a fifth application of the resiniferatoxin was made to each of the pre-treated mice and to each of five untreated mice. Five pairs of pre-treated and untreated mice were shown to an experimentally blind observer who was asked to indicate which animal of each pair showed the most intense blepharospasm (squinting or closed eyelid) in the treated eye.

The results of the test indicated that initial application of resiniferatoxin to the mouse cornea produced an intense blepharospasm, usually indicated by complete eyelid closure. This effect subsided with each successive application and over time. In each of the five pre-treated-untreated animal pairs, the experimentally blind observer picked the untreated animal as having the more intense blepharospasm five of five times. All of the untreated animals exhibited complete eyelid closure, while none of the pre-treated animals exhibited a similarly intense reaction.

RAT BLADDER MICTURITION TEST

Six female Sprague-Dawley rats, weighing between about 200-250 g each, were divided into two groups of three animals. All animals were anesthetized by administration of ketamine Hcl (100 mg/kg i.p.) supplemented with urethane (1.2 g/kg i.p.) as needed. The urinary bladder of each animal was exposed, catheterized and

attached to a cystometrograph. Each of the two groups were subjected to continuous perfusion of water at the rate of 100 l/min, and were intravesically perfused with resiniferatoxin in ten minute intervals with a twenty minute rest between resiniferatoxin perfusions. The first group of three animals was perfused with 1×10^{-5} mg/ml resiniferatoxin. The second group of three animals was perfused with 1×10^{-6} mg/ml resiniferatoxin.

Control cystrometrograms were taken of all animals during an initial water-only perfusion period of approximately 80 minutes to determine a normal micturition pattern for each animal. The cystrometrograms were continuously run throughout the perfusion cycle on each animal. Each group was administered a total of five resiniferatoxin perfusions.

The micturition pattern of the first group indicated an immediate excitatory stage where the average number of bladder contractions increased from approximately 1.25 per minute to approximately 3 per minute. The second perfusion of resinifera-toxin caused a decrease in the number of bladder contractions to approximately 1.85 per minute. The third perfusion of resiniferatoxin caused a delay in the onset of micturition for approximately six minutes, followed by contractions approximately one-half as forceful at a frequency of about 4.7 per minute. The fourth perfusion of resiniferatoxin produced no excitatory micturition response and during the interval between the fourth and fifth resiniferatoxin perfusions, no micturition response was noted. The fifth perfusion of resiniferatoxin also induced no micturition response from the urinary bladder.

The second group of rats exhibited an initial excitatory response to the first perfusion of resiniferatoxin from the control micturition pattern of approximately 1.38 contractions per minute to approximately 1.5 contractions per minute. The second perfusion of resiniferatoxin achieved approximately 1.6 contractions per minute, while the third perfusion of resiniferatoxin achieved approximately 1.1 contractions per minute. The fourth perfusion of resiniferatoxin induced the micturition pattern to return to control levels at approximately 1.3 contractions per minute; in the interval between administration of the fourth and fifth perfusions of resiniferatoxin, the micturition pattern was approximately that of the control period. The fifth perfusion of resiniferatoxin did not alter the micturition pattern. Immediately after the second, third, fourth and fifth perfusions of resiniferatoxin the cystometrograms indicated a gradual and delayed onset of the micturition response.

At the bladder level, afferent sensory function includes regulation of the micturition threshold. The efferent function is produced through neuropeptide release from peripheral terminals of these sensory nerves and involves activation of local bladder motor responses, regulation of nerve excitability and local control of vascular blood flow and permeability. Thus, alteration of the micturition reflex by intravesical administration of resiniferatoxin clearly indicates the action of resiniferatoxin on the afferent sensory neurons.

By way of the foregoing test results, which are intended merely as examples not to limit the scope and content of the present invention, those skilled in the art will recognize that

administration of resiniferatoxin to afferent neural systems, by topical, somato-topical and visceral routes, induces a desensitization of the afferent sensory neurons thereby inhibiting the neuronal response.

Finally, the initial irritant activity of resiniferatoxin may be alleviated by administration of resiniferatoxin in an admixture with an local anesthetic or in by successive administration of a local anesthetic followed by administration of resiniferatoxin. It is known that local anesthetics act by temporarily blocking peripheral neurotransmission. The local anesthetic effect is short lived, will rapidly wear off and will still permit resiniferatoxin to desensitize the type C-fibers for a more prolonged period of time. Local anesthetics are not specific to resiniferatoxin sensitive neurons. Therefore, the local anesthetic effect will be more wide spread, but shorter in duration relative to resiniferatoxin desensitization. Examples of typical local anesthetics which may be combined with administration of resiniferatoxin are procaine, cocaine, lidocaine, tetracaine, mepivicaine and etidocaine. The selected local anesthetic may be present in the pharmaceutical formulation with resiniferatoxin, as previously described, with the anesthetic being present in a concentration range of about 0.001% to about 10% weight/volume of the preparation.

Pharmaceutically acceptable carriers may be used in conjunction and in composition with resiniferatoxin. Pharmaceutical compositions containing the active ingredient can be in the form of creams, ointments, jellies, solutions, suspensions, nasal or inhalant sprays or drops, eye drops, or pressurized or non-

pressurized dispersible powders. For administration to the mucosa, it is preferred to use the active ingredient in solution in a sterile aqueous vehicle which may also contain other solutes such as buffers or preservatives, as well as sufficient quantities of pharmaceutically acceptable salts or of glucose to make the solution isotonic. In addition, when the above composition is intended for use as mucosal administration, it may also contain small amounts of a pharmaceutically acceptable surface-active agent to ensure rapid absorption by the mucosa. Examples of such surface-active agents are polysorbate 80 (Tween 80), benzalkonium chloride, bile salts such as sodium glycocholate, dioctyl sodium sulphosuccinate (Aerosol OT), and the like.

Additionally, aqueous suspensions can be used containing the active ingredient in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxyproplymethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth or gum acacia; and dispersing or wetting agents such as naturally-occurring phosphatides, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with lone chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids with a hexitol, for example polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. The aqueous suspensions

may also contain one or more preservatives, for example ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions can also be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspension may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Pressurized or non-pressurized dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent and a suspending agent; one or more preservatives can be employed.

We Claim:

1. A composition for neuronal desensitization, comprising a pharmacologically acceptable carrier and resiniferatoxin present in an amount of no less than about 1×10^{-11} weight/volume percent of the carrier.

2. The composition for neuronal desensitization according to claim 1, wherein said resiniferatoxin present in an amount in a range of about 1×10^{-11} weight/volume percent to about 2.0 weight/volume percent of the carrier.

3. The composition for neuronal desensitization according to claim 1, wherein said composition further comprises a local anesthetic present in an amount in a range of about 0.001 weight/volume percent to about 10% weight/volume percent of the composition.

4. The composition for neuronal desensitization according to claim 3, wherein said local anesthetic is selected from the group consisting of procaine, cocaine, lidocaine, tetracaine, mepivicaine and etidocaine.

5. A method for desensitization of sensory neurons, comprising applying a therapeutically effective amount of resiniferatoxin.

6. The method for desensitization of sensory neurons

according to Claim 3, wherein said method further comprises topical application of said therapeutically effective amount of resiniferatoxin.

7. The method for desensitization of sensory neurons according to Claim 4, wherein said topical application further comprises application of said resiniferatoxin to mucosal membranes.

8. The method for desensitization of sensory neurons according to Claim 4, wherein said topical application further comprises application of said resiniferatoxin to buccal mucosa.

9. The method for desensitization of sensory neurons according to Claim 3, wherein said method further comprises visceral application of said therapeutically effective amount of resiniferatoxin.

10. The method for desensitization of sensory neurons according to Claim 4, wherein said topical application further comprises somatic topical application.

11. The method for desensitization of sensory neurons according to Claim 8, wherein said somatic topical application further comprises applying said resiniferatoxin to the skin.

12. The method for desensitization of sensory neurons according to Claim 7, wherein said visceral application further comprises intravesical administration of resiniferatoxin into the bladder.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US90/02688

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5): A61K 31/335
U.S. CL.: 514/452

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	514/452,817,818

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X,E	US,A, 4,939,149 (BLUMBERG), 03 JULY 1990. See entire document.	1-12
A	US, A,3,730,960 (WATCHUNG ET AL.), 01 MAY 1973. See entire document.	4,7,8 and 10-12
X	CHEMICAL ABSTRACTS, Volumne 91, No. 19, issued 05 NOVEMBER 1979 (SCHMIDT ET AL.), "INVESTIGATIONS INTO THE SKIN IRRITANT PROPERTIES OF PESINIFERONOL ORTHO ESTERS". See entire document.	1-3

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IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
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International Searching Authority [1]	**Signature of Authorized Officer [20]**
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